QUALITY CONTROL IN CLINICAL STUDIES

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I. Need for quality control (after Hulley SB and Cummings SR, Designing Clinical Research, Williams and Wilkins, Baltimore, 1988)

A. To assure quality of data and avoid systematic bias or random error leading to erroneous or uninterpretable results

B. Missing data

1. Can be disastrous if affects large proportion of measurements

2. If missing in non-random way (and almost always are) leads to bias in results

3. Often biases toward null but not always

4. Examples: echocardiographic LV mass, pulmonary function, treadmill exercise, white cell differential count

5. Best way to deal with missing data is to prevent it from occurring

C. Inaccurate or imprecise data

1. Often remains undiscovered, especially if measurements made by more than one person

2. Typically due to inappropriate technique (poor calibration, biased interrogation, rushed or sloppy measures), often distributed randomly with regard to participant characteristics

3. Less often but more concerning are systematic differences in measurement techniques associated with participant characteristics: obese or poorly-fit persons allowed to hold hand-rails in exercise testing, persons with emphysema permitted to shorten exhalation time in spirometry testing

II. Quality control of clinical procedures

A. Steps that precede study

1. Develop manual of operations

    a. Clear operational definitions of eligibility, recruitment, measurement procedures

    b. Standardized instruments and forms
    c. Approaches to analyzing data

2. Train and certify research team

3. Establish procedures for monitoring data quality

B. Steps during study

1. Conduct quality control procedures on regular schedule throughout the study

2. Provide steady and visible leadership

3. Hold regular staff meetings

4. Reward staff for finding quality control "opportunities"

5. Avoid casting blame which encourages staff to hide errors

6. Maintain minimum schedule of performances of procedures (e.g., at least once per week) to maintain certification

7. Recertify research team periodically

8. Tabulate measures by technicians, compare variability, means

III. Examples of quality control procedures

A. Use of zero muddler to record blood pressure

B. Duplicate lab determinations

C. Repeat independent readings of EKGs

D. Use of second evaluator when treating physician is aware of treatment assignment

E. Special committee to code cause of death

F. Edit of data for missing, inconsistent, illegible, or outlier values

G. Spot checks or repeats of interviews, exam findings, etc.

IV. Identifying appropriate data for quality control

A. Cost of controlling everything is prohibitive

B. May need less attention in blinded, randomized clinical trials as random errors should be distributed evenly between treatment groups

C. Focus on patient safety factors, key exposure variables, and outcome measures

1. Patient safety

a. Consent forms and consent process

b. Integrity of randomization scheme

c. Effects and side-effects of treatment (blood pressure in antihypertensive trial, coagulation measures in anticoagulation trial, etc.)

d. Drug administration (correct drug and dosage, correct code on participant bottle)

2. Major risk factors such as smoking, alcohol intake, cholesterol level

3. Subclinical or clinical disease assessments

a. Ultrasound measurements of atherosclerosis: central reading, blinded to participant characteristics, duplicate measures to assess inter- and intra-reader reproducibility

b. Tissue diagnosis of cancer: duplicate readings of all or sample of pathology specimens

V. Study procedures for quality control

A. Check forms for omissions or major errors while subject still in clinic

1. No errors or transpositions of ID number

2. ID number, name code, study name on each page

3. No missing entries or faulty skip patterns

4. Entries legible

5. Values of key variables within permissible range: SBP < 90 mmHg in blood pressure trial would merit re-checking

6. Values of key variables are consistent with each other: hysterectomy or estrogen use in men

B. Program computer to flag missing or out-of-range values

C. Ensure accuracy of participant ID number with check digit or duplicate entry

D. Enter data in duplicate or check accuracy of entry by hand in random sample

E. Examine frequency distributions periodically to identify aberrant values or less than expected degree of variability

F. Credos

1. To err is human (except in determination of primary outcome, especially if it is death)

2. No one purposely sets out to collect poor quality data

3. Data which are collected without any ongoing quality checks are best left uncollected

VI. Data editing

A. Should be completed prior to data analysis, though often errors crop up only once data begin to be used

B. Internal consistency and validity programs available or can be developed

1. Detect recording, coding, entry errors (hysterectomy in men)

2. Identify missing files

3. Identify missing codes

C. Types of errors

1. Non-normative (clearly wrong) errors-- usually easy to detect

a. Inconsistent or illegal codes (for yes/no or 0/1 data, sex=3; death=4, etc.)

b. Missing values (find out why missing-- must have ongoing editing of forms, best done immediately after completion while participant still available)

c. Outliers-- plot and examine (see below)

2. Normative errors

a. Data entry, transcription errors

b. Extremely difficult to detect

1. Check each value with data form or record

2. Enter data twice and compare files-- unlikely to make same data entry error twice

3. Take random sample and verify with data form or record

D. Identification of outliers

1. Widely differing values for one or a few individuals requires scrutinizing data to be sure no coding, data entry or recording errors occurred

2. Outlier test (Tukey)

a. Rank data, divide into percentiles (quartiles)

b. Identify 25th, 75th percentiles, difference between them (interquartile range

c. Define upper limit as 75th percentile plus interquartile range

d. Define lower limit as 25th percentile minus interquartile range

e. Reanalyze without outliers, report both

3. Easier to exclude data if reason for extreme value is known

4. Prudent judgement should prevail

VII. Bias: Any process at any stage of inference which tends to produce results or conclusions that differ systematically from the truth

A. Minimal requirements for a bias-free study

1. Establish comparable study groups which are free of selection bias

2. Use standard treatment procedures which are reproducible

3. Develop data collection schedule where probability of observing an event, given that it has occurred, is the same for all patients

B. Standardization as a means of bias control

1. Manual of operations

2. Description of treatment procedure

3. Standard definitions

4. Standard equipment

5. Standardized data forms with check lists

C. Checks for bias

1. Periodic checks on baseline comparability of study groups

2. Breakdowns in the random allocation process

3. Differential rate of treatment refusals
4. Differential rate of dropouts
5. Unnecessary unmasking
6. Questionnaire to check on efficacy of masking at end of study
7. Protocol violations which are differential by treatment group
8. Differences in variance of readings by treatment group

D. "Correction" for bias

1. No method of adjustment available
2. Early detection important
3. Purging of data may be necessary
4. Stopping of trial may be necessary
5. Reporting in publications is essential

QUALITY CONTROL IN CLINICAL TRIALS

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Lecture Assessment

1. For which of the following types of data is concurrent quality control least important? {circle one}

   a. Participant eligibility criteria

   b. Measurement of adverse drug effects

   c. Standardized assessment of outcomes such as electrocardiographic interpretation or tissue diagnosis of cancer

   d. Assessment of key exposure variables such as blood pressure

2. A major systematic difference is detected in spirometry testing from one clinic, such that pulmonary function is measured significantly lower in that clinic than all others. What steps can be taken to determine whether this is a true difference or one due to error? {check all that apply}

   a. Observe clinic procedures for conformance with protocol

   b. Examine distribution of data for excessive or insufficient variability

   c. Check equipment calibration logs and observe calibration procedures

   d. Examine characteristics of participants in this clinic to determine whether they differ systematically from other clinics in ways that would lead to lower pulmonary function